PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:
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PCT

NOTIFICATION OF TRANSMITTAL OF INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Rule 71.1)

Date of Mailing *(day/month/year)*	13 JAN 2004
Applicant's or agent's file reference JHU1870WO	**IMPORTANT NOTIFICATION**

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US03/07879	12 March 2003 (12.03.2003)	12 March 2002 (12.03.2002)

Applicant

THE JOHNS HOPKINS UNIVERSITY

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices)(Article 39(1))(see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

Name and mailing address of the IPEA/US Mail Stop PCT, Attn: IPEA/US Commissioner for Patents P.O. Box 1450 Alexandria, Virginia 22313-1450 Facsimile No. (703) 305-3230	Authorized officer Valerie Bell-Harris for Dr. Kailash C. Srivastava Telephone No. (571)-272-0700

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference JHU1870WO	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/US03/07879	International filing date *(day/month/year)* 12 March 2003 (12.03.2003)	Priority date *(day/month/year)* 12 March 2002 (12.03.2002)
International Patent Classification (IPC) or national classification and IPC IPC(7): A61K 49/00; C12N 9/00; C12Q 1/00, 1/48, 1/68, 1/70 and US Cl.: 424/9.2; 435/4, 5, 6, 15, 183		
Applicant THE JOHNS HOPKINS UNIVERSITY		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 6 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of — sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☒ Priority
   - III ☐ Non-establishment of report with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
07 October 2003 (07.10.2003)	22 December 2003 (22.12.2003)
Name and mailing address of the IPEA/US Mail Stop PCT, Attn: IPEA/US Commissioner for Patents P.O. Box 1450 Alexandria, Virginia 22313-1450 Facsimile No. (703) 305-3230	Authorized officer Valerie Bell-Harrison Dr. Kailash C. Srivastava Telephone No. (571)-272-0700

Form PCT/IPEA/409 (cover sheet)(July 1998)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/US03/07879

I. Basis of the report

1. With regard to the **elements** of the international application:*

☒ the international application as originally filed.

☒ the description:
pages 1-47 as originally filed
pages NONE, filed with the demand
pages NONE, filed with the letter of _____.

☒ the claims:
pages 48-55, as originally filed
pages NONE, as amended (together with any statement) under Article 19
pages NONE, filed with the demand
pages NONE, filed with the letter of _____.

☒ the drawings:
pages 1-5, as originally filed
pages NONE, filed with the demand
pages NONE, filed with the letter of _____.

☐ the sequence listing part of the description:
pages NONE, as originally filed
pages NONE, filed with the demand
pages NONE, filed with the letter of _____.

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.
These elements were available or furnished to this Authority in the following language _____ which is:

☐ the language of a translation furnished for the purposes of international search (under Rule23.1(b)).

☐ the language of publication of the international application (under Rule 48.3(b)).

☐ the language of the translation furnished for the purposes of international preliminary examination(under Rules 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

☐ contained in the international application in printed form.

☐ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority in written form.

☐ furnished subsequently to this Authority in computer readable form.

☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. ☒ The amendments have resulted in the cancellation of:

☒ the description, pages NONE

☒ the claims, Nos. NONE

☒ the drawings, sheets/~~fig~~ NONE

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).**

** Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17).*
*** Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.*

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.

PCT/US03/07879

II. Priority

1. ☐ This report has been established as if no priority has been claimed due to the failure to furnish within the prescribed time limit the requested:

   ☐ copy of the earlier application whose priority has been claimed (Rule 66.7(a)).

   ☐ translation of the earlier application whose priority has been claimed (Rule 66.7(b)).

2. ☐ This report has been established as if no priority has been claimed due to the fact that the priority claim has been found invalid (Rule 64.1).

Thus for the purposes of this report, the international filing date indicated above is considered to be the relevant date.

3. Additional observations, if necessary:

V. Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. STATEMENT

Novelty (N)	Claims	1-75	YES
	Claims	NONE	NO
Inventive Step (IS)	Claims	NONE	YES
	Claims	1-75	NO
Industrial Applicability (IA)	Claims	1-75	YES
	Claims	NONE	NO

2. CITATIONS AND EXPLANATIONS

Please See Continuation Sheet

Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

V. 2. Citations and Explanations:

Claims 1-75 lack an inventive step under PCT article 33 (3) as being obvious over Campbell et al. (U.S. Patent 6,255, 062) in view of Mills (U.S. Patent 5,773,592), Loeb et al. (US Patent 5,512,431) and Torkkeli et al (U. S. Patent 5,665,585).

Campbell et al. teach a mammalian, i.e., rat reverse trancriptase enzyme (i.e., beta DNA polymerase or DNA polymerase beta having an activity only in presence of Mn++. Campbell et al. also teach that mammalian DNA polymerase betas are inhibited by phosphate (Column 2, Lines 36-47). Campbell et al., further teach that said activity is expressed in a variety of yeast genera (i.e., Candida, Hansenula, Kluyveromyces, Pichia, Saccharomyces, Schizosaccharomyces and Yarrowia) and mammalian cells (Column 9, Lines 21-36). Campbell et al further teach that dideoxynucleoside triphosphate (i.e., ddNTP) inhibits yeast DNA polymerase beta in presence of Mn++ or Mg++, said enzyme activity is measured in presence of both polyribonucleotide and polydeoxyribonucleotide templates and within a yeast cell (Table 2 and Table3), and said enzyme is also sensitive to sulfhydryl blocker N-ethylmaleimide (Column 4, Lines 60-67 and Column 19, Lines 61-65). Since Campbell et al. teach that ddNTP inhibits a DNA polymerase beta, said enzymes are also mammalian enzymes and function within a cell in presence of Mn++ or Mg++, said determination being carried out according to standard methods known in the art, Campbell et al., intrinsically teach a method to modulate reverse transcriptase activity in a mammal or a yeast or eukaryotic cell, in presence of a poly ribo- or deoxyribo-nucleoside template contained in a tube, well or other reaction vessel as is known in the pertinent art. Furthermore, since the prior art reference teaches determining via radiometry (counting the radioactivity in scintillation counter (Column 19, Lines 46-51) said intracellular activity of said enzyme in a Saccharomyces cerevisiae (i.e., yeast) cell, in presence of Mn++ or Mg++, in presence of same templates and employing same steps as claimed in the instant invention, Campbell et al. (i.e., prior art reference) intrinsically teach the instantly claimed invention.

Campbell et al. however, do not teach that the protein transporting Mn++ comprises a P-type ATPase, wherein said ATPase is a PmrIp protein or homolog thereof, said reverse trancriptase is a retrovirus transcriptase, retrotransportable element comprises a transposon, wherein the retrovirus is human immunodeficiency virus, a method to treat a retrovirus infection in a human subject by administering an agent that alters the manganese ion transport in a retrovirus infected cell, wherein subject is a human and infected cell is a T-lymphocyte.

Mills discloses that besides the enzymes of regulatory pathways or metabolic functions, cellular proteins responsible for transportation, for e.g., Ca++, K+ and Na+ ATPase, small ions such as Ca++, viral replicative enzymes or other enzymes from pathogens are one of the important class of exploitation-prone drug receptors. Such receptors may be applicable for antiviral activity of HIV virus (Column 1, Line 52 to Column 2, Line 14) for example to inhibit HIV reverse transcriptase to treat acquired immunodeficiency syndrome (Column 128, Lines 45-49).

Loeb et al. teach treatment of human immunodeficiency virus in a subject in need thereof, with application of an agent that modulates Mn++ transport in a retrovirus transcriptase (i.e., RT), wherein said retrovirus is a human immunodeficiency virus

Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

(HIV), said transcriptase is an HIV transcriptase (HIV-RT) and said agent is azidothymidine (AZT). Loeb et al. also teach that efficiency for said treatment is evaluated via evaluating the activity of HIV-RT ((Column 2, Lines 40-556; Column 3, Lines 46-56;Column 8, Lines16-33, Column 15, Line59 to Column 16, Line 4; Column 18, Lines 10-30 and Column 19, Lines 10-34). None of the above references teach that said retrotransportable element comprises a transposon. Torkkeli et al., teach a retroviral vector transposon (Column 14, Lines 48-63).

Thus, at the time, the claimed invention was made, an artisan of ordinary skill in the art would have been motivated to develop a method to assess an inhibitor of a yeast/ mammalian/human/ rat reverse transcriptase inhibiting Mn++ transportation protein by assaying said activity in a yeast or a mammalian cell, wherein said transportable protein may be an ATPase, is a transposon and said inhibitor is applicable for the treatment of human immunodeficiency virus infected human T-lymphocyte by inhibiting the activity of human immunodeficiency virus reverse transcriptase, said inhibitor being azidothymidine (AZT) according to the teachings of Campbell et al., in combination with teachings from Mill, Loeb et al., and Torkkeli et al., because Mill remedies the deficiency of ATPase as the metal ion transporting protein, Loeb et al. remedy the deficiency of retrovirus reverse transcriptase, wherein reverse transcriptase is HIV-RT and treating an HIV infected human T-lymphocyte by inhibiting HIV-RT via administration of AZT and Torkkeli et al. remedy the deficiency of transportable protein element comprising a transposon in Campbell et al's teachings. None of the prior art references cited above teach the metal ion ATPase to be Mn++ or Mg++ ATPase or the ATPase to be a PmrIp protein or homolog thereof that is claimed in the instantly claimed invention. However, adjustment of particular conventional working conditions (e.g., certain divalent metal ion or a certain type of ATPase protein etc.) is deemed merely a matter of judicious selection and routine optimization of a result-effective parameter that is well within the purview of the skilled artisan. In view of the fact that the applicant's invention also recites a method and a composition comprising the same steps and ingredients, applicant's invention is obvious over the teachings of Examiner-cited prior art references and therefore, is neither novel, nor has an inventive step.

---------- NEW CITATIONS ----------

NONE

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NOTE OF INFORMAL COMMUNICATION WITH THE APPLICANT

(PCT Rule 66.6)

International application No.	Applicant's or agent's file reference	Date of informal communication *(day/month/year)*
PCT/US03/07879	JHU1870WO	08 December 2003 (08.12.2003)

Applicant
THE JOHNS HOPKINS UNIVERSITY

Communication
- ☒ by telephone
- ☐ personal

Participants — ☒ Identity checked ☐ authorization checked ☐ personally known
- ☐ Applicant:
- ☒ Agent: Ms. Mary Gillette
- ☒ Examiner(s): Dr. Kailash C. Srivastava

Summary of communication:

Applicant's Agent authorized the Examiner to go directly to International Preliminary Examination Report (i.e., IPER/409).

☐ ~~An extension of time limit is granted (Form PCT/IPEA/427.~~

☒ A copy of this note is being sent to the applicant with Form ~~PCT/IPEA/429.~~ PCT/IPEA/424.

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